REMARKS

Claims 1-20 are pending in the application. Claims 8-19 were withdrawn from consideration, leaving claims 1-7 and 20 subject to examination. Claims 1-7 and 20 were rejected under 35 U.S.C. § 112, first paragraph (enablement and written description), and claims 1-6 and 20 were rejected under 35 U.S.C. § 102(a). Each of the rejections is addressed below. First, Applicants note that, as was required by the Examiner, the hyperlinks on page 8 of the application have been deleted.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-7 and 20 were rejected under § 112, first paragraph for lack of enablement. In addition, these claims were rejected under § 112, first paragraph as lacking sufficient written description, as well as for including new matter. This rejection is respectfully traversed.

Applicants first address the new matter rejection, which appears to be based on the prior amendment to claim 1 to include that the method of this claim can be used to determine whether a test subject "may have or be at risk of developing" a titin-related disease or condition of the heart. The Examiner questions what is meant by this addition, as the claim already specifies that the method can be used to determine whether a test subject "has or is at risk of developing" such a disease or condition.

In response, Applicants note that the amendment was made to address a concern raised in an Office Action in the parent application, U.S. Serial No. 09/759,508. In that application, the Examiner had raised a concern as to the predictability of the claimed method in making a definitive diagnosis and stated, in a telephone conference with the undersigned, that

consideration may be given to an amendment stating that the method can be used to determine whether a test subject "may" have or be at risk of a titin-related disease or condition of the heart. It is for this reason that the present application was filed, with the claims amended as they were.

Applicants submit that no new matter is added by this amendment, as the phrase at issue in the claim, "may have or be at risk of developing" (emphasis added), is supported in the application as filed. For example, on page 7, lines 1-3, it is stated that, using the claimed method, "it is possible to detect an increased likelihood of heart disease..." (emphasis added). This passage supports the questioned amendment, as it makes clear that the methods of the invention can be used to determine whether a subject "may" have or "may" be at risk of developing heart disease, as the statement of an "increased likelihood" indicates an increased chance of disease (consistent with the term "may"), rather than an absolute, definitive diagnosis. The presently claimed invention may thus be used, for example, in combination with other diagnostic methods for heart diseases or conditions, to provide confirmation or more information as to the cause of the diseases or conditions. Indeed, Applicants submit that diagnosis of many diseases or conditions often employs the use of multiple assay systems. In view of the above, Applicants request that the new matter rejection be withdrawn.

Applicants further note that new claims 21-32 have been added. New claim 21 is drawn to a method including the same steps as claim 1, but specifies that the method is for use in determining whether a test subject has an increased likelihood of a titin-related disease or condition of the heart, or facilitating determination of the etiology of an existing heart condition. Claims 22-32 depend from claim 21. Applicants request consideration of these claims, particularly in the event that the Examiner maintains that the prior amendment to claim 1 adds

new matter. Although Applicants submit that amended claim 1 does not include new matter, claim 21 has been added because it specifies uses that are literally supported in the application as filed. For example, determination of an increased likelihood of a titin-related disease or condition is literally set forth on page 7, lines 1-3, and facilitation of the determination of the etiology of a heart disease or condition is literally set forth on page 7, lines 5-7. No new matter has been added by these amendments.

Turning now to the enablement rejection, the Examiner refers to Applicants' definition of "titin gene," which includes nucleic acid molecules that encode proteins that have as low as 45% identity to the sequences of human or zebrafish titin proteins. The Examiner states that the term "titin gene" in the claims, thus, includes mutants, allelic variants, and homologs of titin from any source, and that such molecules have not been taught in the specification. This basis for the rejection under § 112, first paragraph has been met by the present amendment to claim 1, which now states that the titin gene that is analyzed in the claimed method is a naturally occurring titin gene. Support for this amendment can be found throughout the specification, for example, at page 2, lines 5-11, where it is stated that the invention includes a method for determining whether a test subject has or is at risk of developing a titin-related disease or condition, by analyzing a nucleic acid molecule of a sample from the test subject. Additional support for this amendment can be found, for example, on page 3, where it is stated that a "titin nucleic acid molecule" is a nucleic acid molecule that encodes a titin polypeptide (lines 22-24), and that a "polypeptide" is a chain of two or more amino acids constituting all or part of a naturally or non-naturally occurring polypeptide (lines 6-9).

The Examiner further states that the precise locus of the pickwick mutation is not

provided in the specification and, thus, that the term "pickwick mutation" has been interpreted as including any mutation that is responsible for the pickwick phenotype. The Examiner further states that the teaching of only a single mutation that is associated with a weak heartbeat in zebrafish is insufficient to provide those of skill in the art with a basis for correlating that any substitution, deletion, or insertion in the titin gene would result in any disease or condition, including heart failure. The Examiner thus concludes that it would require undue experimentation to practice the claimed invention, because it would require a large study including subjects with a large number of diseases or conditions, and that it is unpredictable which mutations would have an effect. Applicants respectfully disagree with this basis for the rejection.

Applicants respectfully submit that analysis of the sequences of titin genes from patients and the correlation of any detected mutations with a disease or condition of the heart would not require undue experimentation. This is shown, for example, in the Satoh paper (Biochem. Biophys. Res. Com. 262:411-417, 1999), which was cited in the rejection under § 102(a) (see below). In particular, Satoh analyzed the sequences of titin genes from eighty-two patients and identified a mutation in a titin gene that correlated with hypertrophic cardiomyopathy. All that was required to achieve this was PCR analysis of a blood sample from each of the patients, gel fractionation of the PCR products, and sequencing of any products having aberrant sizes, as compared to controls. Thus, Satoh shows that analysis of titin gene sequences of numerous subjects, using standard methods, could be carried out to identify mutations associated with heart disease, and that such analysis would not require undue experimentation.

Further support for the fact that carrying out the methods of the present claims would not

have required undue experimentation can be found in the Itoh-Satoh et al. (Biochem. Biophys. Res. Com. 291:385-393, 2002) paper cited by the Examiner. In particular, this paper describes a study in which the occurrence of dilated cardiomyopathy (DCM) was correlated with three mutations in the titin gene. The Examiner stated that this paper shows that one titin polymorphism, Arg328Cys, present in DCM patients was also present in healthy control subjects. In response, Applicants submit that this finding does not negate the fact that detection of mutations in titin can be correlated with disease and conditions of the heart without undue experimentation, because it was simple for Itoh-Satoh to determine the relevance of this mutation to DCM by analysis of control sequences. Thus, this paper supports the importance of the titin gene in heart disease, as was first discovered by the present Applicants, and also shows that characterization of mutations in titin does not require undue experimentation.

The Examiner cites Garvey et al., Genomics 79:146-149, 2002, in this rejection, for teaching that titin is differentially spliced into cardiac (N2B) and skeletal (N2A) isoforms, and that a mutation in mouse titin that disrupts the N2A domain is not associated with cardiac muscle pathology. In response, Applicants submit that it is understood that not every mutation in titin will lead to a disease or condition of the heart. However, Applicants have shown that this protein is important for proper function and development of the heart, and submit that the present discovery properly forms a basis for diagnosis of diseases or conditions of the heart based on mutations in this gene. Determination of whether a particular mutation has a strong correlation to disease can readily be carried out, without undue experimentation, by comparison of test sequences to those of healthy controls, as was done, e.g., in the Itoh-Satoh paper. Thus, Applicants submit that the teachings of Garvey do not support a rejection for lack of enablement.

Applicants further note that claims 21, 22, 32, and 33 specify that the mutation is in a cardiac-specific exon (claims 21 and 32), such as the N2B exon (claims 22 and 33). The teachings of Garvey certainly are not relevant to these claims.

The Examiner also cites Siu et al., Circulation 99:1022-1026, 1999, for teaching that five variations were found in the N2B region of human titin, and that they were determined not to be disease-causing mutations. As is discussed above, the present claims do not require that the detection of a mutation in titin be an absolute diagnosis of heart disease. Rather, detection of such a mutation can be just one factor in a diagnosis (hence the use of the terms "may" and "likelihood" in the claims). Further, the determination of whether any particular mutation is associated with disease can be determined without undue experimentation, as shown in the Itoh-Satoh and Siu papers. Thus, if anything, the Siu paper supports enablement of the present claims.

The Examiner further comments on the teachings of the prior art with respect to conservation of sequences and regions within titin across species, noting that Itoh-Satoh shows, for example, that there are differences in the Z line region between chicken and human titin sequences. In response, Applicants note that it is not unusual for there to be differences between the sequences of different species for a given gene, and that the determination of whether a mutation exists is done by comparison with a naturally occurring sequence of the gene within the given species. Further, Applicants point the Examiner to claims 5 and 29, which specify that the test subject is a human.

The Examiner further states that the specification has not established a universal correlation between any mutation in any titin gene and an association with any disease or

condition of the heart. In response, Applicants note that a universal correlation should not be required. The present Applicants have made the first connection between titin mutations and a phenotype consistent with heart disease. On the basis of this discovery, it is reasonable to predict that detection of mutations in titin may correlate with diseases and conditions of the heart. Applicants thus request that this rejection be withdrawn.

Applicants also point to new claims 21-32, which specify a method for determining whether a subject may have an increased likelihood of a heart disease or condition, or for facilitating determination of the etiology of an existing disease. These methods do not require an absolute diagnosis, as it appears the Examiner requires for the method of claim 1. Rather, these methods can be used, possibly in combination with other methods, to provide an assessment of a subject as to their likelihood of having a heart disease or condition. Applicants request consideration of these new claims.

Applicants respectfully request that the rejection under § 112, first paragraph for lack of enablement be withdrawn, because undue experimentation is not required for those of skill in this art carry out the claimed invention, as is discussed above.

Claims 1-7 were also rejected under § 112, first paragraph for lack of written description. This rejection is respectfully traversed.

The Examiner first states that the term "titin gene," as defined in the specification, includes proteins that have as little as 45% sequence identity to the human or zebrafish titin protein, and thus that this term includes mutants, allelic variants, and homologs, from any source, that have not been described in the specification, which describes only a single mutation. The Examiner thus concludes that the specification provides insufficient written description of the

genus of titin genes or mutations that are encompassed by the claims.

In response, Applicants first note that claim 1, from which the other rejected claims depend, has been amended to specify that the titin gene that is analyzed using the claimed methods is a naturally occurring titin gene. Applicants also note that the present claims are drawn to methods of diagnosing diseases or conditions of the heart by detection of mutations in titin genes, and not to mutant titin genes themselves. These methods certainly are adequately described in the specification, which describes obtaining samples from patients and analysis of titin sequences in the samples. It is not necessary for the specification to list every possible mutation that could be associated with these diseases or conditions, as they can easily be identified by comparison with sequences from healthy controls (see above).

The Examiner further comments that the precise location of the pickwick mutation is not provided, but this is not necessary. In particular, the claimed method involves detection of any mutation in a titin gene, as any such mutation (as discussed above) can be characterized for its association with heart disease. The positions of the mutations are not required to meet the written description requirement, as no particular mutations are being claimed. Rather, what is claimed is a method involving assessment of a sequence for the presence of mutations. This method has been described fully, and it is clear that such a method can be carried out without the provision of details as to which positions may be mutated. In particular, Applicants refer to the Itoh-Satoh paper described above, in which titin mutations were identified and characterized by comparison to control sequences.

Also in this rejection, the Examiner refers to a lack of teaching of the necessary common attributes or features of the genus of encompassed nucleic acids and mutations of the claims, and

notes that those of skill in the art would not recognize that the Applicant was in possession of the genus of nucleic acid molecules claimed. Applicants submit that these statements are not relevant to the present claims. Rather, these statements would be more appropriate in a rejection of claims to nucleic acid molecules or proteins themselves, not to methods that involve the detection of mutations. Applicants clearly describe the steps required for carrying out the claimed method, and also provide reference sequences (e.g., human titin). Applicants thus have clearly shown that they invented what is claimed, and this rejection should therefore be withdrawn.

Rejection under 35 U.S.C. § 102(a)

Claims 1-6 were rejected under § 102(a) as being anticipated by Satoh et al. (Biochem. Biophys. Res. Com. 262:411-417, 1999). Applicants request that this rejection now be withdrawn because, as is stated in the accompanying Declaration of inventor Xiaolei Xu, which was submitted in the parent application (U.S. Serial No. 09/759,508), Applicants established a connection between a mutation causing a weak heartbeat and the titin gene, and thus reduced the present invention to practice, prior to the publication date of the Satoh reference.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. In the event that the next Action is not a Notice of Allowance, Applicants respectfully request that the Examiner kindly contact the undersigned by telephone to discuss this case. If there are any charges not covered or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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